Please add the following new claim:

--145. (New) A method of producing a specific binding pair member, which method comprises:

expressing in recombinant host cells a library of nucleic acid sequences encoding a genetically diverse population of polypeptides, which library of nucleic acid sequences is provided by mutating nucleic acid encoding a specific binding pair member which comprises an enzyme or fragment thereof, which enzyme or fragment thereof is able to bind a ligand of said enzyme and is at least 100 amino acids,

wherein said polypeptides encoded by the library are displayed at the surface of filamentous bacteriophage particles, and wherein genetic material of each filamentous bacteriophage particle displaying a polypeptide includes nucleic acid encoding the polypeptide displayed on that particle.--

REMARKS

I. Status of Claims

Claims 44-144 are currently pending. Claims 66-77 and 110-144 were withdrawn from further consideration as being drawn to a non-elected invention. Claims 44-65 and 78-109 are under consideration in the present application and stand rejected under 35 U.S.C. §112 second paragraph, U.S.C. §102(e) and under 35 U.S.C. §103(a). Applicants respectfully traverse the rejections and request reconsideration of the application in light of the comments and amendments presented herein.

II. Formalities

In the amendment presented above, Applicants have updated the current status of parent application 07/971,857 in the specification page 1.

Applicants acknowledge the Examiner's reference to the draftsman's comments and request that the submission of formal drawings to comply with these comments be deferred to such a time as allowable subject matter is indicated.

Applicants also acknowledge the Examiner's reference to the use of trademarks in the specification. The above amendments to the specification address this

objection to the specification.

III. Rejections under 35 U.S.C. §112, second paragraph should be withdrawn.

The Examiner rejected claims 44-65 and 78-109 under 35 U.S.C. §112, second paragraph. Applicants traverse the rejection and address each of the Examiner's points separately herein below.

Claim 44 was rejected under 35 U.S.C. §112, second paragraph for various reasons. In order to most clearly address each of the rejections Applicants have cancelled claim 44 and inserted new claim 145. This new claim clearly indicates that the library of polypeptides is provided by mutating nucleic acid encoding such polypeptides and it provides that the polypeptides are displayed at the surface of filamentous bacteriophage and as such addresses the rejections of claim 44 on page 4 and 5 of paper number 8 of the Office Action.

The Examiner rejected claims 44-47 and claims 78-85 under 35 U.S.C. §112, second paragraph as being incomplete for omitting essential steps. Applicants traverse the rejection. It is the Examiner's position that the step of obtaining a member of a specific binding pair has been omitted. Applicants disagree, the Examiner seems to be using the term "obtaining" as being synonymous with purifying or selecting. This is improper, the method claimed in Claim 44 (now new claim 145) contains all the steps that would be necessary to allow one of skill in the art to gain possession of a specific binding pair member *i.e.* ***obtain*** such an entity. There is no requirement that the entity be in a selected, isolated or otherwise purified form in order to effect such a possession. Thus, Applicants believe there is no omitted step, however, as discussed with the Examiner on August 18, 2000, in order to clarify the matter further, Applicants have provided that claims 145 and 78 to refer to a method of "producing". Using the methods of amended claim 77 or new claim 145, one of skill in the art would have produced a specific binding pair member. Applicants believe that this discussion and amendment negates the basis for the rejection advanced by the Examiner. Applicants request withdrawal of the rejection and reconsideration of the application.

Claims 46-47 and 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99 and 101 were rejected allegedly having insufficient antecedent basis for the term "the gene III capsid." Applicants have amended these claims to refer to "a gene III capsid protein surface

component" to comport with conventional claiming for antecedency.

The Examiner requested clarification of the term "...an individual displayed polypeptide specific binding pair member or a mixed population of displayed polypeptide specific binding pair members associated in respective particles with nucleic acid..." in claim 48. Applicants point out that it is the specific binding pair member that is associated in its respective particle with encoding nucleic acid and that "mixed population of polypeptides" refers to a population of different polypeptides. Applicants have complied with the Examiner's request that claim 48 be amended to recite "... specific binding pair member or specific binding pair members bind..."Applicants believe this is clear from the wording of the claim and respectfully request that the rejection be withdrawn. The Examiner is invited to contact the undersigned representative if further discussion is required.

The Examiner requested clarification of the term "wherein the particles are selected by enzymatic activity" in claim 58. Applicants have amended the claim to refer to "wherein the particles are selected by enzymatic activity of the displayed polypeptide." Applicants believe this amendment clearly indicates that the polypeptides displayed on the surface of filamentous bacteriophage particles may be selected by the enzymatic activity of the polypeptide.

Claims 55, 57 and 94-101 were rejected as being vague by reciting in step (ii) "producing from nucleic acid in step (i) nucleic acid which encodes a specific binding pair member." The Examiner requested additional clarification of this term. Applicants maintain that step (ii) is not vague and that one of skill in the art would recognize that step (ii) simply means that the nucleic acid of step (i) is used to make additional nucleic acid. Methods for doing so are disclosed in the specification and are well known to those of ordinary skill in the art. This issue was discussed with the Examiner in an interview on August 18, 2000, If the Examiner requires further specific discussions regarding this feature she is invited to contact the undersigned representative. The Examiner suggested that Applicants "in claims 55, 57 replace 'a said derivative specific binding pair member' with said 'derivative specific binding pair member'". Applicants point out that claims 55 and 57 do not recite this term and Applicants believe the Examiner intended this remark to refer to claims 61, 63 and 65. Applicant believe that the amendment to claims 61, 63, and 65 which refer to "...producing

said derivative specific binding pair member by expression of nucleic acid produced according to the method of claim..." 60, 62, and 64 respectively, obviates the rejection.

Claims 60-65 and 102-109 were rejected as being vague and indefinite for reciting "...nucleic acid which encodes a derivative specific binding pair member..." Applicants traverse the rejection. The claims are directed to a derivative specific binding pair member which when read in light of the specification and the claims from which these claims depend means a derivative of the specific binding pair member that is functional. The term "functional" with respect to a specific binding pair member is defined throughout the specification *e.g.*, page 30-31. Applicants believe when this claim is viewed in light of the specification disclosure, the claim is clear and definite.

The Examiner also objected to the term "linkage of another molecule" in claims 60-65 and 102-109 stating that it is not clear what this other molecule is. Applicants traverse. At page 35 lines 3-12, Applicants describe in detail what is intended by the term "derivative" where it is stated that for example, the other molecule may be an Fc tail from another source, or a marker such as an enzyme or a fluorescein. Those of skill in the art would understand what is meant by linkage to another molecule in this claim when it is viewed in light of the specification. Moreover, Applicants further point out that these claims are directed to a method. In a method claim, the technical features relate to physical activities. The activity of linking another molecule an isolated molecule has a clear and unambiguous meaning and a skilled person is well aware of whether or not such a linking activity has been undertaken. Moreover, the exact nature of moiety being linked to the specific binding pair member (or a polypeptide chain component thereof) is not significant because it is the act of linking which is covered by the claim. Whilst in a product claim, a precise description of the modified species may be necessary to define what species is protected, in a method claim, it is the act which must be described and the term 'linking' is sufficient to enable a skilled person to determine whether an action is covered by the claim. Applicants submit that the metes and bounds of the action of 'linkage of another molecule' are entirely clear to a person of ordinary skill and there is no requirement for undue experimentation to establish whether a person has conducted the step of linkage of another molecule to the specific binding pair member or a polypeptide chain component thereof.

Applicants believe these claims are clear and definite and request that the rejection be withdrawn.

The Examiner rejected claims 78, 80, and 82 as vague for reciting "...a polypeptide which is a specific binding pair member with ability to bind a complementary ligand..." As Applicants have already discussed with the Examiner, Applicants believe that the amendment to these claims to refer to "...a polypeptide which is a specific binding pair member capable of binding a complementary ligand..." obviates this rejection. Applicants have further amended these claims in accordance with the Examiner's suggestion (page 9 of paper 8, first paragraph, last sentence). In view of the foregoing Applicants submit that the rejection should be withdrawn.

The Examiner rejected claims 103, 105, 107 and 109 stating that it was not clear what is meant by producing by expression from encoding nucleic acid. These claims depend from claims 102, 104, 106 and 108 respectively which refer to a method of producing nucleic acid encoding a specific binding pair member. Claims 103, 105, 107 and 109 are directed to producing a specific binding pair member from the nucleic acid produced according to claims 102, 104, 106 and 108. Applicants believe that amended claims 103, 105, 107 and 109 which refer to "...producing said derivative specific binding pair member by expression of nucleic acid produced according to the method of claim..." 102, 104, 106 or 108 respectively, obviates the rejection.

Applicants have previously discussed these amendments with the Examiner and feel all the issues have been addressed herein above, however, Applicants particularly request that the Examiner contact the undersigned representative should she have any further questions regarding the above comments and amendments. In light of the foregoing amendments and discussion, Applicants believe all the rejections based on 35 U.S.C. §112 second paragraph have been overcome and the claims are in a condition for allowance. Applicants respectfully request withdrawal of the rejection and favorable reconsideration of the application.

IV. Rejections under 35 U.S.C. §102(e) should be withdrawn

The Examiner rejected claim 44, 46, 48-49, 78-81, 86-89 and 94-97 under 35

U.S.C. §102(e) as being anticipated by Dower (U.S. Patent 5,247,908). Applicants respectfully traverse.

In order for a claim to be anticipated, a single item of prior art must disclose ***each*** element of the claim. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q.2d 81, 90 (Fed. Cir. 1986). Moreover, it is well established that when a claimed invention is not identically disclosed in the reference and instead it requires picking and choosing among a number of different options disclosed by the reference, then the reference does not anticipate. *Mendenhall v. Astec Industries, Inc.*, 13 USPQ 2d 1956 (Fed. Cir. 1989). The Dower reference as cited simply does not anticipate any of the claims of the instant invention.

The claims of the instant invention all are directed to a method of producing a specific binding pair member by a method which involves expressing, in recombinant host cells, a library of nucleic acids which encode a genetically diverse population of polypeptides, in which the library is produced by mutating nucleic acid that encodes a specific binding pair member which comprises ***an enzyme or fragment thereof, which is at least 100 amino acids***. Each claim requires this express feature.

Despite the Examiner's extensive characterization of what is disclosed in Dower, and while there is a mention of the term "enzymes" in a laundry list of proteins of interest to Dower (column 3, lines 19-25), Dower provides absolutely no disclosure of an enzyme or a fragment thereof that is at least 100 amino acids. Indeed, the only reference in Dower to any protein of a given length is to be found at column 8 lines 45 through 52, where Dower is prophetically discussing the expression of V_H domains as peptides of up to 120 amino acids. V_H domains are not enzymes or enzyme fragment. Contrary to the Examiner's assertion, this reference does not refer to a specific binding pair member [that] comprises an enzyme or fragment thereof and is at least 100 amino acids of the instant claims. Additionally, Dower does not teach display of an enzyme (or a fragment thereof) greater than about 200 amino acids (*e.g.*, subject matter of claim 45, 82 and 84).

Furthermore, it cannot be argued that the Dower disclosure of catalytic antibodies provides disclosure of an enzyme as claimed in the present invention. It is accepted that reference to the specification is permissible to ascertain the meaning of a given

claim feature. A specific claim feature in the instant invention is that the mutated "...specific binding pair member comprises an enzyme or a fragment thereof...." Referring to the specification, it becomes evident that the term "enzyme" as used in the specification does not encompass antibodies. The definition of specific binding pair members in the specification distinguishes between on the one hand a specific binding pair member that is an antibody and on the other hand a specific binding pair member that is an enzyme (Specification page 27, line 22 through page 28 line 5). Indeed, this distinction between the specific binding pair member being an antibody or an enzyme is maintained throughout the specification (See *e.g.*, page 8, lines 1-2 and 20-23; page 13, lines 1-3 and 5-9; and page 22, line 3-14 and at various other positions in the specification).

The distinction between antibodies and enzymes is particularly emphasized in the specification at page 22, line 3 to page 22, line 14 where, following a discussion of first antibodies and then receptors, it is stated:

> ***Another possibility, is the display of an enzyme molecule or active site of an enzyme molecule on the surface of a phage (see examples 11,12,30,31,32 and 36).*** Once the phage enzyme is expressed, it can be selected by affinity chromatography, for instance on columns derivatized with transition state analogues. If an enzyme with a different or modified specificity is desired, it may be possible to mutate an enzyme displayed as a fusion on bacteriophage and then select on a column derivatised with an analogue selected to have a higher affinity for an enzyme with the desired modified specificity. (***Emphasis added***)

In light of the specification disclosure, one of skill in the art would understand that the term "...specific binding pair member comprises an enzyme ..." as used in the specification and claims does ***not*** include antibodies.

Furthermore, nowhere does Dower suggest starting with one sequence encoding a specific binding member and providing a library of nucleic acid sequences encoding a genetically diverse population of polypeptides ***by mutation***, as is required by the present claims. Dower's statements with respect to other proteins are contained in the following paragraph:

> "The protein for which the DNA is enriched and cloned according to the present invention is typically an antibody or fragment thereof, but may also be

any protein which may be cloned from a nucleotide library. In addition to antibodies, such proteins may include, for example, growth hormones, enzymes, zymogens etc. Proteins which may be cloned are those for which specific binding partners (*e.g.*, antigen or hapten when the desired protein is an antibody) have been identified." Column 3, lines 18 to 27.

Thus, although Dower gives no details of its hypothetical suggestion for a limited range of non-antibody molecules, the reference to "cloning" from a library suggests that Dower envisaged construction of a library from nucleic acid obtained from mammalian cells, with screening against a known specific binding partner to enrich for and obtain ("clone") the desired protein and encoding nucleic acid. The present invention is not directed to "cloning" of that kind, but rather producing a specific binding pair member by means of provision of a library of genetically diverse polypeptides encoded by nucleic acid provided by ***mutation*** of nucleic acid encoding a specific binding pair member (that is an enzyme or a fragment thereof able to bind a ligand and greater than 100 amino acids), which is nowhere suggested by Dower. In light of the above discussion, Applicants submit that the Dower disclosure fails to teach all the claim features of the instant invention.

Given that the Dower reference provides no disclosure of enzymes of at least 100 amino acids, let alone enzymes of about 200 amino acids, or indeed any disclosure of generating specific binding pair members that are enzymes by mutation of a first "parent" enzyme, Dower cannot be said to anticipate the instant claims and Applicants request that the rejection be withdrawn.

V. Rejections under 35 U.S.C. §103(a) should be withdrawn.

Claims 44-65 and 78-109 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Dower (U.S. Patent 5,427,908). Applicants respectfully traverse the rejection.

In order for a given reference to render obvious a claimed invention, that reference must contain a detailed enabling methodology for practicing the claimed invention; a suggestion for modifying the prior art reference to practice the claimed invention and evidence suggesting that the invention would be successful. *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988). Moreover, in order for a *prima facie* case of obviousness to be established,

it must be shown that the prior art, having disclosed all the elements of the claimed invention, also would have suggested to those of ordinary skill in the art that they should make the claimed invention and the prior art is required to demonstrate a reasonable expectation of success of arriving at the claimed invention. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). The suggestion and the reasonable expectation of success must come from the prior art and not from the Applicants' own disclosure. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988)

The Dower reference relied on by the Examiner clearly fails to satisfy both the test set forth by *O'Farrell* and the test set forth by *Vaeck*. More specifically, not only does Dower completely fail to disclose all the elements of the claimed invention, as discussed above, but Dower provides absolutely no motivation or suggestion that ***enzymes*** of about 100 or 200 amino acids could be produced using phage display as described in the present invention. The only discussion that the Examiner is able to point to is that Dower provides a prophetic description of a multichain protein such as an antibody or binding fragments thereof. This disclosure of antibodies does not teach to the instantly claimed invention which is directed to enzymes.

The suggestion or teaching of bacteriophage display of ***enzymes*** having at least 100 amino acids came from the Applicants' own invention and ***not*** from the cited references. Thus, it would appear that the Examiner has used the Applicants' own disclosure as a roadmap to identify the separate elements of the claimed invention in disparate references to allege that these render the claimed invention obvious. Using such hindsight based on the Applicants own disclosure to piece together an obviousness rejection is impermissible. The mere fact that the reference ***can*** possibly be modified is not sufficient to establish a *prima facie* case of obviousness. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990) (see MPEP 2143.01).

In addition, even if one of skill in the art were to review the Dower disclosure and fortuitously attempt to produce an enzyme of about 100 amino acids by phage display, Dower provides absolutely no expectation of success of such an endeavor. Specifically, prior to the present invention, there was a prejudice in the art that it was not possible to display, at the surface of a phage particle, a polypeptide that is larger than about 100 amino acids. For

example, those of skill in the art recognized that the largest size of fragment for display on a filamentous phage should be 100-300 bp (corresponding to 33-100 amino acids). *(See* Parmley and Smith, *Gene* 73, 305-318 (1988) at p. 315). Others stated that "...[I]t has been shown that fusion phage are useful only for displaying proteins of less than 100 and preferably less than 50 residues, because large inserts presumably disrupt the function of gene III, and therefore phage assembly and infectivity...." Bass et al., *Protein: Structure, Function & Genetics* 8, 309-314 (1990) (citing Parmley and Smith, *Gene* 73, 305-318 (1988)). Furthermore, there was no expectation of being able to display a functional, folded protein domain, especially such a domain of larger than 100 amino acids. The present invention overcame the prejudice in the art by providing, for the first time, an enabling disclosure of the bacteriophage display of functional protein domains having at least 100 amino acids.

Dower provides no objective evidence to refute the teachings and overcome the prejudice in the art. Indeed, Dower explicitly recognized that the presence of a large fragment near the N-terminus of the coat protein may cause a decrease in the phage infectivity but then goes on to make a statement that "...larger fragments may still be effectively enriched...." This facile statement does nothing to alleviate the widespread skepticism in the art regarding the possibility of phage display of a polypeptide that is larger than 100 amino acids. This singular statement is devoid of any objective evidence proving that phage display of such larger polypeptides is possible should be weighed against the body of art that specifically and categorically shows that it is not possible to display polypeptides of greater than about 100 amino acids. When such a comparison is made it becomes evident that at the time of the Dower application, the art generally taught away from the idea that it was possible to display larger polypeptides and protein domains at the surface of a filamentous bacteriophage and the lack of recitation of enabling technology in Dower makes this statement merely wishful thinking.

Applicants submit that in light of the teachings in the art, a person of ordinary skill in the art would not have had a reasonable expectation of success of achieving phage display of functional polypeptides of greater than 100 amino acids, given the prejudice in the art against the display of large polypeptides and functional domains on filamentous phage (and the expectation of failure engendered by this prejudice) and further in view of the

absence in Dower of any relevant experimental results and the failure of Dower to overcome such prejudice. Thus Dower fails the *Vaeck* requirements for *prima facie* obviousness and does not render obvious an invention directed to a method of producing a specific binding pair member that comprises an enzyme or a fragment thereof which is at least 100 amino acids.

Additionally, the Examiner states that Dower teaches combining V_H and V_L sequences in a single phage genome and "V_H and V_L together would become more than 200 amino acids." Applicants disagree, while it may be true that Dower makes this statement, Applicants submit that this mere mention does not comport to a teaching that a ***single*** polypeptide of greater than 200 amino acids is displayed.

More particularly, the association between a V_H and a V_L described by Dower does not form a polypeptide of more than 200 amino acids. The V_H domain is one polypeptide and the V_L domain is another polypeptide. The suggestion by Dower, and it is only a suggestion not backed up by any enabling disclosure, is that it is possible to display a multichain protein on the phage surface, ***but*** each chain - *i.e.*, each polypeptide - of the multichain protein ***is less than*** 200 amino acids. The problems associated with breakdown of the phage coat are noted by Dower noted by Dower in column 8 and are part of the difficulties taught by Parmley and Smith (*Gene* 73, 305-318 (1988) at p. 315) and which contributed to the prejudice in the art against it being reasonable to expect success for display of inserts over 100 amino acids (see *e.g.*, Parmley and Smith and Bass papers cited above). Dower itself does not overcome the prejudice in the art, because of its serious flaws and absence of enabling disclosure. It merely states, for example: "Although a large peptide fragment near the N-terminus of the coat protein may cause a decrease in the phage infectivity and/or yield compared to phage with much smaller, similarly-placed fragments, the larger fragments may still be effectively enriched by the procedures described herein." (Column 8, lines 52 to 57).

Where a filamentous bacteriophage coat protein surface component, such as a gene III coat protein surface component, is employed for display of a polypeptide, the concerns in the mind of the skilled person and giving arise to the prejudice already discussed relate to effects on particle assembly. For instance, Parmley and Smith showed that fusions

with a gene III protein cause breakdown of the protein, and consequent aberrant particle formation and infectivity. While it is not an essential feature of the present invention that filamentous bacteriophage particles displaying polypeptides remain infective (although useful), particle formation is required.

In relation to display of a multichain protein comprising V_H and V_L domains, Dower suggests fusion of one chain to a gene III protein, with the other chain to be expressed with a signal peptide lead sequence so it is secreted into the periplasm of the host cell (see Dower, Column 9, lines 3 to 29). Whether or not the nucleic acid encoding the "second chain" (*e.g.* V_L if V_H is expressed as a gene III protein fusion) is included within the phage, only one chain, one (first) polypeptide of much less than 200 amino acids is displayed as a fusion. The other, second polypeptide associates with the first polypeptide following expression in soluble form (***i.e. not as a fusion***). No single polypeptide of greater than 200 amino acids is displayed.

Dower particularly envisages that the cloning strategy utilizing a phage coat protein, will provide expression of a protein chain (or a first polypeptide chain in the case of a multichain protein, *e.g.*, V_H) fused to the N-terminus of a coat protein and transport to the inner membrane of the host where the hydrophobic C-terminal of the coat protein anchors the fusion protein in the membrane in such a way that the N-terminal of the coat protein containing the protein chain protrudes into the periplasmic space to make that protein chain available for interaction with the second chain (*e.g.*, V_L; See Dower Column 9, lines 39-55). As discussed above, the art taught against trying display of a polypeptide of greater than 100 amino acids fused to a gene III protein because of anticipated excessive breakdown of the resulting fusion protein and consequent effects on phage particle assembly (reflected by loss of infectivity). Dower only proposes (and this hypothetically without provision of any enabling disclosure) display using a fusion with a polypeptide of a comparable size (*e.g.*, a VH domain). Given the teaching of Parmley and Smith, the Dower proposal to employ such a fusion protein which subsequently associates with a second polypeptide chain would not have given the skilled person any reasonable expectation of success for display of a much larger fusion partner, namely greater than 200 amino acids. If a polypeptide of greater than 100 amino acids compromises particle formation (*i.e.*, as shown by Parmley and Smith) then

a polypeptide of greater than 200 amino acids, twice the size, would not have been expected to allow for proper particle formation.

Moreover, Dower also fails the *O'Farrell* test for obviousness. As discussed with the Examiner in an interview on August 18, 2000, Applicants provide a copy of the declaration of Nobel Laureate Professor, Sir Aaron Klug, (which was originally submitted to the Patent and Trademark Office during the prosecution of the parent application serial number 07/971,857 (now U.S. Patent No. 5,969,108) as part of a response of 16 July 1996) to substantiate the fact that Dower is not enabled and cannot render obvious the instantly claimed invention.

Sir Aaron is an internationally recognized expert on the interactions of proteins and nucleic acids in systems such as simple viruses, and his declaration clearly demonstrates that a person of ordinary skill in the art attempting to achieve bacteriophage display [of an enzyme or a fragment thereof] using Dower's flawed methodology would fail to achieve display and that such failure would only serve to confirm the existing prejudice in the art against display of polypeptides of more than 100 amino acids and to confirm the expectation of failure engendered by the prejudice. Having confirmed the prejudices, such a person would have no motivation to dissect Dower to identify and correct the many errors contained in that disclosure.

Given the above discussion, namely that Dower does not disclose all the claim features of the present invention, that Dower provides no suggestion of a modification to arrive at the instant invention or any expectation of success of modification of Dower to arrive at the present invention, Applicants believe the instant invention is non-obvious over the art cited and request that the rejection based on Dower be withdrawn.

VI. Conclusion.

Applicants believe all the claims are now in a condition for allowance. Favorable reconsideration of the application is respectfully requested. The Examiner is invited to contact the undersigned with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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October 5, 2000

APPENDIX OF PENDING CLAIMS

45. A method according to claim 145 wherein said enzyme or fragment is at least 200 amino acids.

46. A method according to claim 145 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

47. A method according to claim 45 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

48. A method according to claim 145 wherein particles formed by said expression are selected or screened to provide an individual displayed polypeptide specific binding pair member or a mixed population of displayed polypeptide specific binding pair members associated in respective particles with nucleic acid encoding said displayed polypeptide specific binding pair member or specific binding pair members, the specific binding pair member or specific binding pair members thus provided having ability to bind a complementary ligand.

49. A method according to claim 48 wherein the particles are selected by affinity with a complementary ligand.

50. A method according to claim 49 which comprises recovering any particles bound to said complementary ligand by washing with an eluant.

51. A method according to claim 50 wherein the eluant contains a molecule which competes with said particles for binding to said complementary ligand.

52. A method according to claim 49 wherein the particles are applied to said complementary ligand in the presence of a molecule which competes with said particles for binding to said complementary ligand.

53. A method according to claim 48 wherein the particles are selected by enzymatic activity of the displayed polypeptide.

54. A method of producing a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a selected or screened particle obtained by a method according to claim 48; and

(ii) producing by expression from nucleic acid obtained in step (i) the encoded specific binding pair member.

55. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a selected or screened particle obtained by a method according to claim 48; and

(ii) producing from nucleic acid obtained in step (i) nucleic acid which encodes a specific binding pair member.

56. A method of producing a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a selected or screened particle obtained by a method according to claim 49; and

(ii) producing by expression from nucleic acid obtained in step (i) the encoded specific binding pair member.

57. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a selected or screened particle obtained

by a method according to claim 49; and

(ii) producing from nucleic acid obtained in step (i) nucleic acid which encodes a specific binding pair member.

58. A method of producing a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a selected or screened particle obtained by a method according to claim 53; and

(ii) producing by expression from nucleic acid obtained in step (i) the encoded specific binding pair member.

59. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a selected or screened particle obtained by a method according to claim 53; and

(ii) producing from nucleic acid obtained in step (i) nucleic acid which encodes a specific binding pair member.

60. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a selected or screened particle obtained by a method according to claim 48, said nucleic acid encoding a polypeptide specific binding pair member or a polypeptide chain component thereof; and

(ii) producing from the nucleic acid obtained in step (i) nucleic acid which encodes a derivative specific binding pair member, wherein said derivative specific binding pair member is produced by addition, deletion, substitution or insertion of one or more amino acids, or by linkage of another molecule, to a polypeptide specific binding pair member or polypeptide chain component thereof encoded by the

nucleic acid obtained in step (i).

61. A method of producing a specific binding pair member, the method comprising:

producing said derivative specific binding pair member by expression of nucleic acid produced according to the method of claim 60.

62. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a selected or screened particle obtained by a method according to claim 49, said nucleic acid encoding a polypeptide specific binding pair member or a polypeptide chain component thereof; and

(ii) producing from the nucleic acid obtained in step (i) nucleic acid which encodes a derivative specific binding pair member, wherein said derivative specific binding pair member is produced by addition, deletion, substitution or insertion of one or more amino acids, or by linkage of another molecule, to a polypeptide specific binding pair member or polypeptide chain component thereof encoded by the nucleic acid obtained in step (i).

63. A method of producing a specific binding pair member, the method comprising:

producing said derivative specific binding pair member by expression of nucleic acid produced according to the method of claim 62.

64. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a selected or screened particle obtained by a method according to claim 53, said nucleic acid encoding a

polypeptide specific binding pair member or a polypeptide chain component thereof; and

(ii) producing from the nucleic acid obtained in step (i) nucleic acid which encodes a derivative specific binding pair member, wherein said derivative specific binding pair member is produced by addition, deletion, substitution or insertion of one or more amino acids, or by linkage of another molecule, to a polypeptide specific binding pair member or polypeptide chain component thereof encoded by the nucleic acid obtained in step (i).

65. A method of producing a specific binding pair member, the method comprising:

producing said derivative specific binding pair member by expression of nucleic acid produced according to the method of claim 64.

78. A method of producing a member of a specific binding pair, the method comprising:

contacting a library of filamentous bacteriophage particles with a desired ligand,

wherein said filamentous bacteriophage particles display on their surface a polypeptide which is a specific binding pair member capable of binding a complementary ligand, and each filamentous bacteriophage particle contains genetic material including nucleic acid encoding said polypeptide, which nucleic acid encoding the polypeptide is provided by mutation of nucleic acid encoding a specific binding pair member which comprises an enzyme or fragment thereof, which said enzyme or fragment thereof is able to bind a ligand of said enzyme and is at least 100 amino acids,

wherein said filamentous bacteriophage particles display a population of specific binding pair members, and

separating particles displaying specific binding pair members which bind to

said desired ligand.

79. A method according to claim 78 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

80. A method of producing a member of a specific binding pair, the method comprising:

contacting a library of filamentous bacteriophage particles with a desired ligand,

wherein said filamentous bacteriophage particles display on their surface a polypeptide which is a specific binding pair member capable of binding a complementary ligand, and each filamentous bacteriophage particle contains genetic material including said nucleic acid encoding said polypeptide, which nucleic acid encoding the polypeptide is provided by mutation of nucleic acid encoding a specific binding pair member which comprises an enzyme or fragment thereof, which said enzyme or fragment thereof is able to bind a ligand of said enzyme and is at least 100 amino acids,

wherein said filamentous bacteriophage particles display a population of specific binding pair members, and

separating particles displaying specific binding pair members which have a desired enzymatic activity.

81. A method according to claim 80 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

82. A method of producing a member of a specific binding pair, the method comprising:

contacting a library of filamentous bacteriophage particles with a desired ligand,

wherein said filamentous bacteriophage particles display on their surface a polypeptide which is a specific binding pair member capable of binding a complementary ligand, and each filamentous bacteriophage particle contains genetic material including nucleic acid encoding said polypeptide, which nucleic acid encoding the polypeptide is provided by mutation of nucleic acid encoding a specific binding pair member which comprises an enzyme or fragment thereof, which said enzyme or fragment thereof is able to bind a ligand of said enzyme and is at least 200 amino acids,

wherein said filamentous bacteriophage particles display a population of specific binding pair members, and

separating particles displaying specific binding pair members which bind to said desired ligand.

83. A method according to claim 82 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

84. A method of producing a member of a specific binding pair, the method comprising:

contacting a library of filamentous bacteriophage particles with a desired ligand,

wherein said filamentous bacteriophage particles display on their surface a polypeptide which is a specific binding pair member capable of binding a complementary ligand, and each filamentous bacteriophage particle contains genetic material including nucleic acid encoding said polypeptide, which nucleic acid encoding the polypeptide is provided by mutation of nucleic acid encoding a specific binding pair member which comprises an enzyme or fragment thereof, which said enzyme or fragment thereof is able to bind a ligand of said enzyme and is at least 200 amino acids,

wherein said filamentous bacteriophage particles display a population of specific binding pair members, and

separating particles displaying specific binding pair members which have a desired enzymatic activity.

85. A method according to claim 84 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

86. A method of producing a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 78; and

(ii) producing by expression from nucleic acid obtained in step (i) the encoded specific binding pair member.

87. A method according to claim 86 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

88. A method of producing a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 80; and

(ii) producing by expression from nucleic acid obtained in step (i) the encoded specific binding pair member.

89. A method according to claim 88 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

90. A method of producing a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 82; and

(ii) producing by expression from nucleic acid obtained in step (i) the encoded specific binding pair member.

91. A method according to claim 90 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

92. A method of producing a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 84; and

(ii) producing by expression from nucleic acid obtained in step (i) the encoded specific binding pair member.

93. A method according to claim 92 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

94. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 78; and

(ii) producing from nucleic acid obtained in step (i) nucleic acid which encodes a specific binding pair member.

95. A method according to claim 94 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in

another filamentous phage.

96. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 80; and

(ii) producing from nucleic acid obtained in step (i) nucleic acid which encodes a specific binding pair member.

97. A method according to claim 96 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

98. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 82; and

(ii) producing from nucleic acid obtained in step (i) nucleic acid which encodes a specific binding pair member.

99. A method according to claim 98 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

100. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 84; and

(ii) producing from nucleic acid obtained in step (i) nucleic acid which

encodes a specific binding pair member.

101. A method according to claim 100 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

102. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 78, said nucleic acid encoding a first specific binding pair member or a polypeptide chain component thereof; and

(ii) producing from the nucleic acid obtained in step (i) nucleic acid which encodes a derivative specific binding pair member, wherein said derivative specific binding pair member is produced by addition, deletion, substitution or insertion of one or more amino acids, or by linkage of another molecule, to said first specific binding pair member or polypeptide chain component thereof encoded by the nucleic acid obtained in step (i).

103. A method of producing a specific binding pair member, the method comprising:

producing said derivative specific binding pair member by expression of nucleic acid produced according to the method of claim 102.

104. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 80, said nucleic acid encoding a first

specific binding pair member or a polypeptide chain component thereof; and

(ii) producing from the nucleic acid obtained in step (i) nucleic acid which encodes a derivative specific binding pair member, wherein said derivative specific binding pair member is produced by addition, deletion, substitution or insertion of one or more amino acids, or by linkage of another molecule, to said first specific binding pair member or polypeptide chain component thereof encoded by the nucleic acid obtained in step (i).

105. A method of producing a specific binding pair member, the method comprising:

producing said derivative specific binding pair member by expression of nucleic acid produced according to the method of claim 104.

106. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 82, said nucleic acid encoding a first specific binding pair member or a polypeptide chain component thereof; and

(ii) producing from the nucleic acid obtained in step (i) nucleic acid which encodes a derivative specific binding pair member, wherein said derivative specific binding pair member is produced by addition, deletion, substitution or insertion of one or more amino acids, or by linkage of another molecule, to said first specific binding pair member or polypeptide chain component thereof encoded by the nucleic acid obtained in step (i).

107. A method of producing a specific binding pair member, the method comprising:

producing said derivative specific binding pair member by expression of nucleic acid produced according to the method of claim 106.

108. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 84, said nucleic acid encoding a first specific binding pair member or a polypeptide chain component thereof; and

(ii) producing from the nucleic acid obtained in step (i) nucleic acid which encodes a derivative specific binding pair member, wherein said derivative specific binding pair member is produced by addition, deletion, substitution or insertion of one or more amino acids, or by linkage of another molecule, to said first specific binding pair member or polypeptide chain component thereof encoded by the nucleic acid obtained in step (i).

109. A method of producing a specific binding pair member, the method comprising:

producing said derivative specific binding pair member by expression of nucleic acid produced according to the method of claim 108..

145. A method of producing a specific binding pair member, which method comprises:

expressing in recombinant host cells a library of nucleic acid sequences encoding a genetically diverse population of polypeptides, which library of nucleic acid sequences is provided by mutating nucleic acid

encoding a specific binding pair member which comprises an enzyme or fragment thereof, which enzyme or fragment thereof is able to bind a ligand of said enzyme and is at least 100 amino acids,

wherein said polypeptides encoded by the library are displayed at the surface of filamentous bacteriophage particles, and wherein genetic material of each filamentous bacteriophage particle displaying a polypeptide includes nucleic acid encoding the polypeptide displayed on that particle.